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A Review on Transfersomes: Promising Carrier for Transdermal Drug Delivery

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ORIGINAL ARTICLE

A Review on Transfersomes: Promising Carrier for Transdermal Drug Delivery

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ABSTRACT – The transdermal drug delivery systems (TDDS) facilitate over the traditional techniques by including the capability to transport the drugs more selectively to a certain point; more straightforward, more precise, and minimum frequent dosing besides decreasing inconsistency in systemic drug concentrations. Additionally, these administration methods are painless and self-administered, improving patient compliance and offering a regulated drug release. The skin's outmost layer, known as stratum corneum (SC), serves as a barrier for only unionized molecules and molecules with less than 500 Da molecular weight making it a solid obstacle for TDDS. As a result, this technique can only be used to deliver a specific quantity of medications. In this case, some possible alternatives are used to overcome this challenge as a chemical permeation enhancer, iontophoresis, sonophoresis, microneedles, electrophoresis, and vesicular system such as liposome, transfersome, ethosome, etc. One of these methods, known as transferosomes, appears to be the most promising since it enables the encapsulation of pharmaceuticals that are hydrophilic, lipophilic, and amphiphilic with more penetration efficiency than traditional liposomes. Transfersomes may squeeze and bend themselves as undamaged vesicles through tiny holes and are much smaller than their original size due to their elastic nature. However, the concept of transfersomes, their composition, their mode of action, and numerous preparation methods are all covered in this review to deliver information to future researchers. This evaluation also emphasizes contemporary transfersome applications and their advantages and disadvantages. This evaluation also clarifies the potential applications for inspiring scientists to produce more ground-breaking findings in the future.

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INTRODUCTION

Recently, numerous novel strategies like iontophoresis, electrophoresis, sonophoresis, chemical permeation enhancers in the formulation, microneedle, and vesicular systems (liposome, transfersome, ethosome) have been adopted successfully for enhancing the transdermal delivery of bioactive molecules as well as drugs and the results are encouraging [1], [2]. Transfersomes as novel drug carriers have already gained much interest because of their exceptional physico-chemical characteristics. Gregor Cevc coined the phrase "Transfersome" and the underlying idea in 1991 [3]. In the broadest sense, a transfersome is a complex aggregation, which is exceptionally responsive to stress and flexible. As an ultra-deformable vesicle, it is a preferred to form flexible structure with a complex lipid bilayer around an aqueous core. Also, the vesicle facilitates self-regulating and self-optimizing due to the local composition's interdependence and bilayer shape [4]. Therefore, this makes it possible for the transfersome to easily penetrate various transport obstacles before acting as a carrier of drugs for prolonged release of therapeutic medicines and non-invasive targeted therapeutic agents administration [5]. Transfersomes are composed of phospholipids such as phosphatidylcholine and surfactants, where Span 80, sodium cholate, deoxycholate, dipotassium, and Tween 80 are the surfactant examples. This has increased the use of transdermal administration for systemic effects and enabled treatment optimization for locations linked to the skin and underlying tissues [6], [7]

Afore discussed matter indicates that the transdermal drug delivery system using transfersome is a promising approach. So, based on the current research advancement, we need to perform an extensive literature study by aggregating updated information to expedite the development of an effective TDDS. For this, we performed a review study on the composition of transfersomes, preparation technique, application prospects, besides benefits and drawbacks of it to deliver valuable information to future researchers.

COMPOSITION OF TRANSFERSOMES

Phospholipids (such as soy phosphatidylcholine, egg phosphatidylcholine, etc.) make up the majority portion of transfersome compositions, along with 10 – 25% surfactants/edge activators (such as sodium deoxycholate, sodium cholates, Spans, and Tweens), ethanol or methanol 3 – 10% as alcohol, and a total lipid concentration equivalent of ≤ 10% in the suspension of final aqueous lipid [8]. In this instance, the aqueous solvents were first employed to self-assemble phospholipids or amphipathic components (phosphatidylcholine) into a lipid bilayer, forming a lipid vesicle

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simply [2]. Second, a bilayer softening element (such as an amphiphile medication or a biocompatible surfactant) raises the permeability and flexibility of the lipid bilayer. Therefore, transfersome vesicle can consequently adapt its form without difficulty and swiftly by adjusting the bilayer's component local concentration to the local stress [9]. Such properties of transfersome exceptionally differ from conventional vesicles and acts as outstanding adjustable and deformable artificial membrane [10]. However, the details are presented in Figure 1.

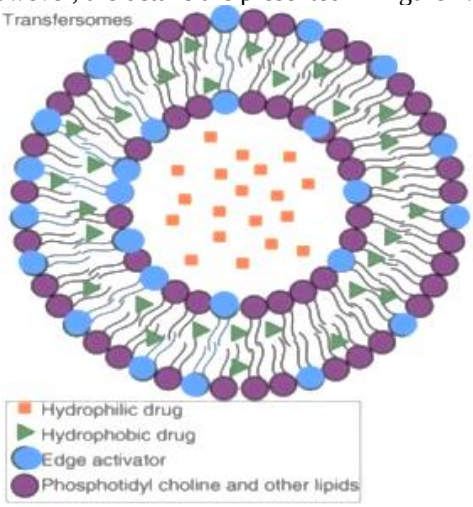

Figure 1: Transfersomes's Structure [11].

MECHANISM OF TRANSFERSOMES

Transfersomes carry drugs either intracellularly or transcellularly through the stratum corneum. "Osmotic gradient or transdermal gradient" has been reported as the main mechanism for penetration of transfersomes through the skin [3]. Where the vesicles are a type of colloidal particles that form an amphiphilic bilayer. Generally, in the internal aqueous compartment, the vesicular drug delivery service systems carry the hydrophilic drugs, although, within the lipid bilayer, the hydrophobic drugs are entrapped [7]. However, transfersomes are self-optimizing and ultra-flexible due to the higher deformability of therapeutic agents carrier vesicles, which facilitate passageway across skin by associating with the tissue layer versatility of the transferresome and its ability to maintain integrity [10], and the details are presented in (Figure 2).

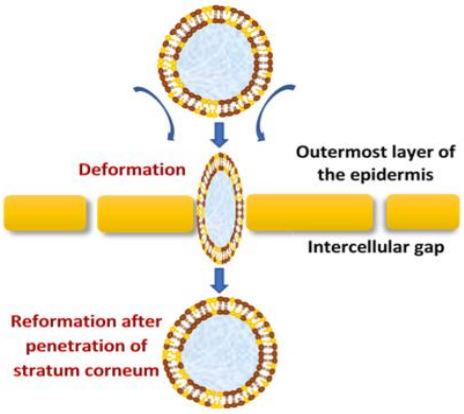

Figure 2: Mechanism of Transfersomes [8].

They penetrate across the intact epidermis efficiently if it is applied under the nonocclusive conditions. This precise (nonocclusive conditions) condition of the skin is required to trigger the transepidermal osmotic gradient over the skin. Based on the study by Cevc and Blume reveals that, the hydrotaxis (xerophobia) is the penetration mechanism of transfersomes, which is defined as the moisture-seeking preference of transferosome toward deeper skin layers rather than the dry outer backdrop due to moisture loss from the transfersomal formulation after application to the skin (nonocclusive condition). In this case, because of the natural transdermal gradient, such transdermal water activity difference appears, generating heavy force to widen the intercellular junctions with minimum resistance and generating 20–30 nm transcutaneous channels to pass the transfersomes vesicles through the skin. The mentionable matter is that transfersomes may achieve lipid bilayer permeability and flexibility as supramolecular entities that are composed of a least amphipathic agent besides an edge activator as a bilayer-softening agent. Furthermore, the osmotic gradient occurs due to water evaporation over the skin's surface due to the generation of body heat. Then, it acts as a driving force for carrying therapeutic agents to the desired point from applied areas with minimal toxicity. Therefore, transfersomes

exhibits outstanding permeation efficacy to cross numerous barriers (over skin's small channels) than liposomes, which are available conventionally though it has a similar bilayered structure with the facility of encapsulation of lipophilic, amphiphilic, and hydrophilic drugs [12]. Additionally, some specific transfersomes may have little propylene glycol or ethanol as alcohol to enhance the penetration capabilities as well as cosolvents. In this case, the intercellular lipid matrix fluidity could be increased by ethanol and later decrease the lipid lamellae's density. As a result, it can pass through the SC and reach the targeted locations, such as the dermis or blood circulation [3], [8].

PREPARATION TECHNIQUES

Transfersomes can be prepared by modified handshaking process, thin film hydration process, vortexing-sonication process, reverse-phase evaporation process, centrifugation process, suspension homogenization process, ethanol injection process, and high-pressure homogenization process [13].

Thin Layer Hydration

The thin layer hydration process is an easy and straightforward method to produce on a laboratory scale, which is held by two stages, i.e., preparation of the thin film and hydration of the thin film [14]. Initially, the phospholipid and antioxidants need to be dissolved in ethanol with surfactant and later put into a circular flask [15]. After that, a rotary vacuum evaporator (i. e., Buchi R- 100, Switzerland) needs to be used to evaporate the solution at 40° C and will be deposited in the vacuum at a speed of 150 rpm. The solvent must be evaporated in the icebox overnight after forming a thin layer. On the other hand, phosphate buffer solution needs to be added at 37° C to produce the moisturized dry lipid film for 45 min at a speed of 50–250 rpm. In this case, the temperature enhances phospholipids' stability and the active ingredient in the hydration process [16]. If the temperature is too high, the encapsulation efficiency of the transfersome will certainly be affected. Their thermal insecurity is also well known to proteins and peptides. After the hydration process, lipid bilayer vesicles and lamellarity, i.e., multilamellar vesicles/MLV, are formed in numerous sizes using phospholipids. The obtained MLV as transfersomes could appear as a milky white suspension [17]. Then, the vesicles are swollen and cooled at room temperature. Finally, passing it through a sandwich of 100 to 200 nm polycarbonate filters, the sonicated vesicles are homogenized [8].

Vortexing-Sonication

In the vortexing-sonication process, the medicine, phospholipids, and edge activators are combined in a phosphate buffer solution. Then, the mixed solution is vortexed until it forms like a suspension of milky transfersomal. Later, at room temperature, it is sonicated for a particular time using a bath sonicator before being extruded by 450 and 220 nm polycarbonate films/membranes [8]. For example, the vortexing-sonication process was used in [18] to produce the RES-loaded transferosomes. RES (10 mg) was mixed with soya lecithin and surfactant in this case. Then dissolve it in a 2:1 ratio with chloroform/methanol and vortexed for around10 minutes. In a desiccator, the resultant mixture was allowed to dry to create a thin film for 24 hours at room temperature. Afterwards, pH 5.5 enabled 10 ml simulated nasal fluid (SNF) was used instead of oleic acid as a permeation enhancer to hydrate obtained thin film and replace the soya lecithin successfully. The mentionable matter is that, at room temperature, the resulting vesicles were allowed to expand for around 2 hours before being vortexed for 20 minutes. Then, a probe sonicator was used to minimize the size of the obtained vesicle for 20 min, and a further 0.2-μm Sartorius membrane filter (GMBH, Germany) was used three times to gain sufficient size of vesicles. Before washing the vesicles with simulated nasal fluid, a cooling centrifuge was used to cool and separate the vesicles. Then stored at 4°C, the prepared transferosomes for future use.

Modified Handshaking

The essential idea of the modified handshaking technique is the same as that of the thin film hydration method. In this case, the lipophilic drug, the organic solvent, and the edge activator are combined with the phospholipids in a round-bottom flask. All excipients of this mixer should be dissolved in the solvent perfectly, besides yielding a transparent and clear solution. The obtained organic solvent is then extracted through handshaking evaporation rather than a rotating vacuum evaporator. Meanwhile, the round-bottom flask must partially be submerged in a high-temperature water bath (for example, 40-60 °C), and finally, the thin lipid coating forms inside the flask wall [8].

Centrifugation Process

Inside the natural solvent, the phospholsipids and lipophilic medicine with edge activator need to be dissolved. Then, the solvent should be evaporated at the desired temperature and under reduced pressure. Under vacuum pressure, the solvent's remaining residues should also be removed. Then obtained lipid film is centrifuged at room temperature and hydrated with the appropriate stream solution. In this stage, the hydrophilic drugs could be incorporated with the obtained lipid and swollen, besides further sonication to obtain multilamellar lipid vesicles [8].

Suspension Homogenization Method

An adequate quantity of edge activator needs to be combined with ethanolic phospholipid solution to make transfersomes by suspension homogenization method. Then the produced solution is mixed with buffer to determine the total lipid content. Then, the final formulation is twice as often sonicated, frozen, and thawed [8].

Reverse-Phase Evaporation

The edge activator and phospholipids need to be appropriately dissolved using diethyl ether and chloroform as an organic solvent mixture in a round-bottom flask for reverse-phase evaporation. Then after, the lipophilic drug needs to be mixed with this solution and obtain lipid films by evaporating via a rotary evaporator. Then diethyl ether and/or isopropyl ether are used to redissolve the obtained lipid films as an organic solution. Later, the hydrophilic drug is appropriately mixed and then sonicated by a bath sonicator till it forms homogeneous water in oil emulsion. Finally, a rotary evaporator slowly evaporated the organic solvent forming a viscous gel as the suspension of vesicular [8].

Ethanol Injection

The ethanol injection process's organic phase is created by dissolving the lipophilic medication, edge activator, and phospholipid in ethanol. Then it is magnetically stirred for the appropriate amount of time until a clear solution is achieved. The water-soluble compounds are dissolved in the phosphate buffer to generate the aqueous phase. This step allows for introducing hydrophilic drugs and is heated at 45-50 degrees Celsius. The ethanolic phospholipid solution was dropwise injected into the aqueous solution and continuously stirred for the specified period. Finally, the ethanol is removed using a vacuum evaporator and sonicating to minimize allowable particle size [8].

High-Pressure Homogenization

The phospholipids, edge activator, and medication in the high-pressure homogenization process is equally disseminated in distilled water or PBS, including alcohol, then ultrasonically shaken and concurrently agitated. After that, the solution is exposed to intermittent ultrasonic shaking perfectly. A high-pressure homogenizer is subsequently used to homogenize the resultant mixture. Finally, the transfersomes are kept under the proper conditions [8].

APPLICATIONS OF TRANSFERSOMES

Delivery of insulin

Insulin-loaded transfersomes provide the medication through the skin barrier that is non-compromised using a reproducible drug effect. The same or better results have been achieved in patients who are receiving an infusion of insulin therapy or solution [19].

Corticosteroids

Transferosomes are also used to supply corticosteroids to patients. Transferosomes increase the specificity of site and drug safety of corticosteroid delivery service into the skin. Corticosteroids structured on transferosomes are biologically lively at doses several times below the current formulation for epidermis diseases [20].

Proteins and peptides

Widely, the transfersomes have been used for protein and peptide transfer as a promising carrier. These are big biogenic molecules and complicated to transfer into the designated spot; they are destroyed in the GI tract when taken orally. The use of transferosomes to overcome these problems is the best solution. Again, after multiple skin challenges, the delivery of the adjuvant immunogenic serum albumin using transferosomes is showed good efficiency that is equally active immunologically as the equivalent injected proteo-transferosomes preparations [20].

Interferon

Transferosomes have also been utilized to transport interferons, such as leukocytic-derived interferon- (INF), which is a naturally occurring protein with antiviral, antiproliferative, and immunomodulatory properties. However, transferosomes-based TDDS has the potential to provide regulated medication while also enhancing the stability of labile medicine [20].

Anti-cancer drugs

Using transfersome technology, anti-cancer medicines such as methotrexate were attempted for transdermal distribution. The outcomes were favourable [21]. This provides a novel therapy strategy, particularly for skin cancer [20].

Anaesthetics

In less than 10 minutes, anaesthetics in transferosome suspension generate a topical anaesthetic. The maximal following pain insensitivity (80%) is comparable to a subcutaneous bolus dosage, although the duration of action of transferosomal anaesthetics has longer. [22]. When compared to previous formulations, a transfersomal formulation containing PAMAM G3 increased local anaesthetic effectiveness by 1.62 times [23].

Additionally, transferosomes are used for NSAIDs, herbal drugs, and transdermal immunization purposes. However, the application of Transfersome with their formulation and preparation techniques is presented in Table 1.

Table 1. Application of transfersomes with their formulation and preparation techniques

Transfersome formulation	Preparation Techniques	Applications	References
Tacrolimus-loaded transfersomes	Thin film dispersion-hydration technique	To treat atopic dermatitis	[24]
Capsaicin-loaded transfersomes	Conventional thin film hydration technique	For the treatment of Rheumatoid arthritis (RA)	[25]
Apigenin-loaded transfersomes	Modified rotary evaporation sonication method	For the treatment of skin cancer	[26]
Cilnidipine loaded transfersomes	Conventional thin layer evaporation and sonication technique	To treat hypertension	[27]
Aceclofenac-loaded transfersomes	Thin film hydration method	For the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis	[7]
Curcumin-loaded transfersomes	Modified thin-film hydration	For the treatment of RA	[15]
Carbopol-based miltefosine-loaded transfersomal gel	Ethanol injection method	For the treatment of cutaneous leishmaniasis (CL)	[28]
Carvedilol Loaded Nano-Transfersomes	Thin-film hydration method	For Skin Cancer Treatment	[29]
Trolamine salicylate loaded transfersomes	Solvent evaporation method	For the treatment of inflammatory muscle, tendon and joint diseases	[30]
Imatinib Loaded Transfersomal gel	Thin film-hydration method	To treat RA	[31]
Vitamin C enriched Adapalene-loaded transfersome gel	Reverse-phase evaporation	for the treatment of Acne vulgaris	[32]
Rifampicin and Vancomycin Co-loaded transfersomal gel	Modified handshaking method	For the management of CL	[33]
Docetaxel-loaded folate-modified TPGS-transfersomes	Thin-film hydration and extrusion method	To treat glioblastoma multiforme	[12]
Mupirocin loaded transfersomal gel	Thin film hydration method	For the management of impetigo.	[34]
Quercetin loaded transfersomes	Thin film hydration method	For wound healing treatment	[35]
Asiatic acid loaded transferosomal gel	high-pressure homogenization technique	For the prevention of scars and different types of skin disorder	[36]
Vitamin D3 loaded transfersomes	Ethanol injection method	For the supplement of vitamin D3 as a health benefit	[37]
Curcumin loaded transferosomal gel	Conventional rotary evaporation method	For the treatment of Alzheimer's disease (AD)	[38]
Efinaconazole-loaded transfersomes	conventional rotary evaporation method	For the healing of nail infection	[39]
Tofacitinib Citrate-loaded transferosomal gel	Rotary evaporation and sonication technique	For the treatment of skin cancer	[40]
5-Fluorouracil and Etodolac Co-loaded transfersome hydrogel	Thin film hydration technique	For oral cancer treatment	[41]
Ivabradine HCl loaded transfersomes	Modified ethanol injection approach	To treat stable angina pectoris	[42]
Chitosan-insulin-transfersomes	Thin film hydration technique	For the treatment of AD	[43]
Lornoxicam loaded transfersomal hydrogel	Thin film hydration technique	For the treatment of local inflammatory disease	[44]
Lidocaine-loaded transfersomes	Thin film hydration technique	Substitute to the painful local anesthetic injection	[45]
Tocopherol-loaded transfersomes	High-Pressure Homogenization technique	For the purpose of wound dressing	[46]
Itraconazole loaded transfersomes	Ethanol Injection method	To treat fungal infection	[47]

Ofloxacin loaded transfersomal nanovesicles	Thin film hydration method	For the management of bacterial meningitis	[48]
Hydroquinone-loaded transfersomes	Thin film hydration method	To treat hyperpigmentation	[49]
Nystatin loaded transfersomes	Thin film hydration technique	For the treatment of vulvovaginal candidiasis	[50]
tinidazole-loaded transfersomal gel	Thin-film hydration method	For the treatment of bacterial Vaginosis	[51]
Acetazolamide loaded transfersomes	Ethanol Injection method	To treat glaucoma	[52]

BENEFITS AND DRAWBACKS

Transferosomes offer benefits over other vesicular systems, including their strong skin penetration power, higher stability, capacity to release drugs systemically, and maximum deformability than the avaiable vesicular systems like ethosomes, niosomes, etc. but the production and processing of transfersomes are both quite pricey.

Benefits

- Transdermal treatment using transfersome provides a continuous infusion of a substance over a long length of time [9], [46].
- Transdermal drug input using transfersome can have a comparable therapeutic effect with a lower daily dosage of the medication than is required [8].
- It facilitates drugs with narrow therapeutic windows [9].
- Longer duration of effect, resulting in less frequent doses [8].
- Increased convenience to drug administration [9].
- Improved bioavailability [8], [42], [46].
- It has higher consistent plasma levels, which helps to maintain the plasma concentration of potent drugs [8].
- The ability to stop medication administration by merely removing the patch from the skin [9].
- Due to excellent compliance and comfortability, it is a painless, simple application, and non-invasive [9].
- It also enhances therapeutic efficacy [8].

Drawbacks

- It exerts slow therapeutic benefits for hydrophilic structures on the skin [9], [53].
- It is not feasible or beneficial for lower-potent drugs [8].
- Not appropriate for high drug doses [8].
- It has a huge possibility of changing the adhesion properties with patch type and environmental conditions [9].
- There is a higher possibility of skin irritation for sensitive skin [8].
- The high production cost is also a significant drawback [9].
- Because of oxidative degradation properties, transfersomes are chemically unstable [8].

CONCLUSION

Transfersomes are specially made vesicles that may respond to stress by squeezing through pores in the skin that are much smaller than their own, increasing the transdermal flow of the therapeutic substances. It is evident that transfersomes can more effectively carry tiny and big therapeutic substances into and through the skin. However, this literature study studied the composition of transfersoms and their mechanism of action to deliver the drugs. We also briefly studied the preparation of various techniques, and applications besides benefits and drawbacks to motivate future researchers to use transfersomes as transdermal drug delivery carriers and advance drug delivery technology as well. Finally, this review leads us to the conclusion that transfersomes will have a wide range of future uses.

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